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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/492,392	Applicant(s) Commercon
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Sep 16, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 17-35 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 17-35 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 18 (filed 9/16/02), claims 20-26, 32, 33 have been amended, and claims 34-35 added. Claims 17-35 remain pending.

Applicants' arguments filed 9/16/02 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the factors for evaluating the need for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As indicated previously, the following references disclose either or both of the following: (a) compounds that failed to inhibit bacteria and (b) that compounds which failed to inhibit bacteria were minor structural variants of compounds that do inhibit

bacteria:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

In response to previous arguments, applicants have pointed to *In re Marzocchi* (169 USPQ 367, 1971) which states the following:

> "Specification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding in scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 USC §112 unless there is reason to doubt objective truth of statements contained therein which must be relied on for enabling support; **assuming that sufficient reason for such doubt exists, a rejection** for failure

to teach how to make and/or use **will be proper** on that basis; such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling".

While *Marzocchi* sets forth the proposition that an examiner bears the initial burden of raising doubt about an applicants assertions, *Marzocchi* does not in any way "immunize" an applicant from enablement rejections.

Next, applicants have argued that the examiner has disregarded their previous arguments with respect to 35 USC §101. However, if an applicant makes an argument that is moot, and the examiner characterizes it as such, the examiner has met his burden with regard to the argument in question. The point has been emphasized several times in the previous Office actions that a rejection under 35 USC §101 has not been imposed. As a general proposition, if an examiner abstains from imposing a given rejection, there is no reason to debate the question of whether such a rejection would have been improper if it had been imposed. Applicants have continued to press the issue of utility by arguing that the examiner believes that doubt exists about whether a compound could exhibit antibacterial activity. Among the most important advances in medicine during the 20th century was the development of antibacterial agents. No reasonable person can deny that numerous compounds exist which inhibit bacterial growth. Accordingly, it is entirely credible that a compound could exist which inhibits bacterial growth. To clarify further, (a) a rejection under 35 USC §101 has not been imposed, (b) a rejection under 35 USC §101 is

not now being imposed, (c) the examiner has not previously characterized as incredible the proposition that an compound could exist which inhibits growth of bacteria, and (d) the examiner does not now characterize as incredible the proposition that an compound could exist which inhibits growth of bacteria. Issues surrounding enablement and utility are not the same. It is routinely the case that a given asserted utility is not incredible, and at the same time, that enablement is lacking. Such is the case here. Applicants have also cited *In re Brana*. First, the cited passage refers to "utility", rather than enablement, and so it may be dismissed on this basis alone, since no rejection under §101 has been imposed. Second, in *Brana*, the applicants did provide *in vitro* data, and so the Court never had to decide the question of whether an applicant can be required to provide evidence of enablement in cases where no data whatsoever has been provided.

Applicants have questioned the examiners assertion that structure/activity relationships are unpredictable where antibacterial activity is concerned. Applicants have argued that the references are not directly relevant to applicants asserted utility (i.e., (Gavini, Fudou, Juvvadi, and Avrahami). First, the issue is "how to use" the compounds, not utility. The question is, does the specification teach a skilled microbiologist how to use the claimed compounds to inhibit bacterial growth? As it happens, all four of these references do describe attempts to use the disclosed compounds to inhibit bacterial growth. Accordingly, the references are directly relevant to the question of whether one can predict the propensity

of a compound to inhibit bacterial growth merely by viewing its structure.

Next, applicants have asserted that they do not merely predict antibacterial activity. As evidence, applicants have pointed to page 11, line 28+ (specification) which discloses that the compounds are not toxic. However, absence of toxicity should not be equated with efficacy. For example, pure water is not toxic, but if one merely drinks pure water, this will not inhibit bacterial growth.

Next, applicants have pointed to page 11 line 20+, where the following is recited:

"they synergize the antimicrobial activity of pristinamycin".

The examiner offered a response to this assertion in the previous Office action. The previous argument is reproduced below:

> This phrase is very ambiguous, and subject to interpretation. First, it is not clear what "they" refers to. "They" could refer to a mixture of one of the compounds of claim 17 in combination with a "Group B streptogramin". Thus, even if one chooses to interpret the passage in question as an assertion that "they" are synergistic, all of the efficacy (if any) could still reside in the "Group B streptogramin", rather than the compounds of claim 17. Second, it is not clear what is meant by "synergizing". Does this mean that the effective dosage of pristinamycin is reduced when administered in combination with acompound of claim 17 and a "Group B streptogramin"...? If so, this is not necessarily in accord with the asserted utility, which is that of inhibiting bacterial growth. There are many excipients, which are pharmacologically inactive by themselves, but which can enhance the activity of pharmacologically active compounds. Such enhancement can certainly be "useful". But if the claimed compounds do not exhibit antibacterial in and of themselves, enablement is lacking. Third, the presence or absence of "synergy" is something that would have to be subject to scrutiny. For example, suppose that an investigator has two rats, both infected with *S. aureus*, and two compounds, designated "X" and "Y". Compound "X" has been shown definitively to exhibit antibacterial activity, and compound "Y" is untested, and may be inactive. The researcher then administers compound "X" to the first rat, and a mixture of "X" and "Y" to the second. The result is that the first rat dies, and the second rat lives. What would such an experiment mean? Suppose next that the researcher infects forty rats with *S. aureus*, and adminsters compound "X" to rats #1-20, and administers a mixture of "X" and "Y" to rats #21-40. The result is that 12 of rats #1-20 survive, and just 11 of rats #21-40. Is there "synergy"....? Finally, the researcher tests compound "Y" against a colony of *S. aureus* (in a petri dish) and discovers that compound "Y" is entirely inactive. Thus, based on the first experiment (on two rats), a person with no knowledge of probability, statistics, or microbiology might be inclined to believe

that compound "Y" is "synergistic". A more experienced scientist, however, would hold a different view. The point is that one could reach a conclusion of synergy erroneously, especially if the experiments are based on a statistical analysis of numbers of surviving versus dying animals. This is not to say that applicants are "wrong", or that they are "right" (with regard to synergy), only that given the situation, a mere assertion of synergy with nothing more, is not particularly meaningful.

Applicants have thus far declined to respond to the issues raised above. To further underscore the point about the necessity of disclosing data analysis protocol, a copy of each of the following references is provided with this Office action. Each of these references discusses the issue of statistical analysis, and more importantly the issue of artifacts or invalid conclusions that can be drawn from an inadequate experimental design, or flawed assumption:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* **28** (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (*Chronobiology International* 18 (6) 1041-53, 2001).

None of these references "proves" that the assertion on page 11 line 20+ of the specification is invalid. They do, however, raise sufficient doubt as to impose upon applicants the burden

of at least providing experimental details, and an explanation of how the various data were analyzed. Next, applicants have argued that the expense of providing data, whether in vitro or in vivo, would be unduly burdensome. As the claims currently stand, if applicants can show that the compounds are effective to inhibit growth or proliferation of bacteria *in vitro*, that would be sufficient. On the other hand, if applicants choose to rely solely on the assertion that is present on page 11 line 20+, further information would be required, as indicated above.

In accordance with the foregoing, (a) one cannot predict antibacterial activity merely by viewing a structure, and (b) "undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth. It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention.

Each of claims 25-27 is drawn to a process of preparing a Group A streptogramin derivative. Each of these claims encompass both of the following two possibilities: (a) the final product is isolated, and (b) the final product is never isolated. It is to the second of these two possibilities that this ground of rejection is targeted.

At the end of the reaction, one will have a round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and perhaps other impurities. One who is in possession of such a mixture is not in possession of the target compound. Moreover, is not apparent how a chemist who is possession of round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and other impurities is going to use this mixture to inhibit bacteria. The point here is that the specification does not describe how a skilled chemist could use the contents of such a round-bottom flask to inhibit bacteria. If applicants disagree with this assessment, applicants are requested to point to the page and line number where this matter is discussed. For the chemist who is determined to avoid isolating or recovering the compound of formula I, how would he proceed if his objective were to inhibit bacterial growth? Applicants could argue that the chemist who is in possession of the round-bottom flask which contains various compounds could "use" that mixture as a source of the target compound (of formula I). However, the claims at issue are not drawn to a method of preparing a mixture; instead, they

are drawn to a method of preparing a compound of formula I. If there is descriptive support for it, applicants could add a claim which is drawn to a method of preparing a mixture that contains a compound of formula I. But as matters currently stand, the claims are drawn to a method of preparing a *compound*, and the claims encompass the possibility of the chemist abstaining from isolating the compound. The specification does not teach a skilled chemist how to obtain the compound without isolating it. It is suggested that the claims be amended to recite a step for isolation or recovery of the target compound.

*

Claims 25-30 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 25-27 is rendered indefinite by its failure to recite a step for isolating the final product. At the end of the reaction, one will have a round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and perhaps other impurities. One who is in possession of such a mixture is not in possession of the target compound. It is not apparent how a chemist who is possession of round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and other impurities is going to use this mixture to inhibit bacteria. In response to this ground of rejection, applicants have argued essentially that, for all intents and purposes, mixtures are equivalent to pure compounds. However, this is certainly not true. But if applicants really believe that a mixture which contains a compound of formula I is indistinguishable from the compound per se, then applicants should feel no reluctance in adding a step for isolation of the compound of formula I. On the other hand, if applicants recognize that pure compounds are vastly different from mixtures that contain them (regardless of the intended use), then applicants can at least understand the basis for the rejection.

.....

From the perspective of §112, second paragraph, there is no prohibition against claiming a method of preparing a mixture that contains a compound of formula I. If there is descriptive support for it, it is suggested that applicants claim such. Of course, a mixture must contain at least two components; a second component should be specified.

- Claim 25 recites (last three lines) a process of "separating". However, this renders the claim indefinite as to what is being separated from what. To take a simplistic example, suppose that one had four coins, a nickel, a penny, a dime, and a quarter. One could achieve "separation" of the penny in any of several ways, including the following:

  (a) a penny by itself
  (b) a penny and a dime
  (c) a penny and a nickel
  (d) a penny and a quarter
  (e) a penny and a nickel and a quarter
  (f) a penny and a dime and a quarter

  That is, "isolating" the penny is only one of the ways that one could achieve separation. With respect to the instant case, suppose that one had a round-bottom flask which contains four unreacted starting materials, solvent, the"target" compound, and twelve impurities. By removing, e.g., three of those impurities, one could say that one had succeeding in "separating" the target compound from those three impurities. However, this would not be particularly meaningful. It is suggested that the term *recovery* or *isolation* be used. (See also claim 27).

- Claim 26 recites the following: "capable of forming formaldehyde". This renders the claim indefinite as to whether the formaldehyde is ever produced. See also claim 27.

- Claim 27 step (a)(1) recites "a desired R" group". However, this suggests an emotional component to the decision. As it happens, the process of claim 27 can only be used to prepare compounds in which R" is a <u>branched alkyl</u> group. This is

because the reactant must be a ketone, and not an aldehyde. That being the case, claim 27 could be drawn to a process of producing compounds in which R" is a branched alkyl group (only), in which case the ketone could then be specifically defined in terms of R". Of course, if applicants really intended to refer to an aldehyde or a ketone, the analysis would be different.

- Claim 28 makes reference to a "group B streptogramin derivative". Applicants have argued that the specification provides examples of compounds to which this label may be applied. However, (a) the claims should stand on their own, and (b) it is not clear where the dividing line is between compounds that qualify as "group B streptogramin derivatives" and those that don't. For example, if variable R_b (page 9, formula "A") is a phenyl moiety, is the resulting compound a "group B streptogramin derivative"...? It is suggested that the formula that is present on page 9 be introduced into the claim. Further structures may be provided if descriptive support in the specification exists for them. The same issue applies in the case of claims 29-30.

✺

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800